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| | | | HUYNH, PHUONG N | |
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| | | | 1644 | |

DATE MAILED: 10/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | |
|------------------------------|--------------------------|------------------|
| Office Action Summary | Application No. | Applicant(s) |
| | 09/776,232 | KUNDIG ET AL. |
| | Examiner Phuong Huynh | Art Unit 1644 |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE Three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 13 August 2003.

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 38-51,61 and 62 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 38-51,61 and 62 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) Notice of References Cited (PTO-892)

2) Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.

4) Interview Summary (PTO-413) Paper No(s). _____.

5) Notice of Informal Patent Application (PTO-152)

6) Other: _____.

DETAILED ACTION

1. Claims 38-51 and 61-62 are pending are being acted upon in this Office Action.
2. The International Search Report on PTO 1449 filed May 10, 2003 have been considered but crossed out because it is not appropriate for IDS.
3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
4. Claims 38-51 and 61-62 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a method of inducing LCML specific CTL response in a mammal, which method comprises directly injecting a composition comprising a specific peptide antigen wherein the peptide is LCMV-glycoprotein consisting of SEQ ID NO: 569, or a plasmid DNA pEFGPL33A that encodes the immunodominant LCMV-glycoprotein epitope aa31-41 to the lymph node or lymph vessel of the mammal and maintaining LCMV specific CTL response in said mammal, (2) the said method wherein the plasmid is formulated in a composition comprising 1-10% ethyl alcohol, 00-1% benzyl alcohol, 0.25-.5mM EDTA, and a citrate-phosphate buffer of pH 7.4-7.8 consisting of 3-50mM citrate and 90-200 mM phosphate, **does not** reasonably provide enablement for a method of inducing a CTL response as set forth in claims 38-51 and 61-62 comprises delivering a liquid comprising (1) *any* cell-free antigen, (2) *any* protein, (3) *any* peptide, (4) *any* microorganism, (5) *any* nucleic acid encoding *any* undisclosed antigen, and (6) *any* “component” of microorganism cell and wherein said microorganism cell comprises a recombinant nucleic acid encoding or promoting expression of said undisclosed antigen for treating *any* disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working

examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a method of inducing LCMV specific CTL response in a mammal, which method comprises directly injecting a composition comprising a specific peptide antigen wherein the peptide is LCMV-glycoprotein consisting of SEQ ID NO: 569 to the lymph node or lymph vessel of the mammal and maintaining LCMV specific CTL response in said mammal. The specification further discloses a method of inducing LCMV specific CTL response in a mammal, which method comprises directly injecting a composition comprising a plasmid DNA pEFGPL33A that encodes the immunodominant LCMV-glycoprotein epitope aa31-41 formulated in 1-10% ethyl alcohol, 00-1% benzyl alcohol, 0.25-.5mM EDTA, and a citrate-phosphate buffer of pH 7.4-7.8 consisting of 3-50mM citrate and 90-200 mM phosphate for maintaining LCMV specific CTL response in said mammal. The said methods wherein the LCMV specific CTL response is maintained via an osmotic pump implanted in the mammal, or via an insulin pump.

The specification does not teach how to make *any* cell-free antigen mentioned, much less for inducing any CTL response against any antigen for treating any disease because the terms “antigen”, “protein”, and “peptide” without the amino acid sequence and SEQ ID NO have no structure, much less function.

Stryer *et al* teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

There is no recognition in the art that sequence with identity predicts biological function. Attwood *et al* teach that protein function is context-dependent and the state of the art of making functional assignments merely on the basis of some degree of similarity between sequences and the current structure prediction methods is unreliable. Skolnick *et al.*, teach that sequence-based

methods for function prediction are inadequate and knowing a protein's structure does not necessary tell one its function (See entire document, Abstract in particular).

Koga *et al* teach that lymph node injection of antigen such as adjuvant accelerates arthritis than conventional footpad injection in the rat. Furthermore, Koga *et al* teach that lymph node route is more efficient than the conventional route in terms of minimal dose (one fifth of the conventional route) and more consistent appearance of prolonged skin reaction (See abstract, in particular). Given the indefinite number of cell free antigen, protein, peptide and microorganism for the claimed method, it is unpredictable which undisclosed antigen, protein, peptide, microorganisms, the corresponding nucleic acid and/or which component of microorganism cell expressing said undisclosed antigen, protein or peptide is effective for inducing CTL response for treating a specific disease such as cancer and HIV. Since the cell-free antigen, protein, peptide and microorganism for the claimed method is not enabled, it follows that the polynucleotide encoding the undisclosed antigen, protein, or peptide for the claimed method for inducing CTL response for treating any disease is not enabled. It also follows that the method of inducing CTL response wherein the antigen is delivered with any cytokine is not enabled.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

5. Claims 38-51 and 61-62 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of a method of inducing a CTL response as set forth in claims 38-51 and 61-62 comprises delivering a liquid comprising (1) *any* cell-free antigen, (2) *any* protein, (3) *any* peptide, (4) *any* microorganism, (5)

any nucleic acid encoding *any* undisclosed antigen, and (6) *any* “component” of microorganism cell and wherein said microorganism cell comprises a recombinant nucleic acid encoding or promoting expression said undisclosed antigen for treating *any* disease.

The specification discloses only a method of inducing LCMV specific CTL response in a mammal, which method comprises directly injecting a composition comprising a specific peptide antigen wherein the peptide is LCMV-glycoprotein consisting of SEQ ID NO: 569 to the lymph node or lymph vessel of the mammal and maintaining LCMV specific CTL response in said mammal. The specification further discloses a method of inducing LCMV specific CTL response in a mammal, which method comprises directly injecting a composition comprising a plasmid DNA pEFGPL33A that encodes the immunodominant LCMV-glycoprotein epitope aa31-41 formulated in 1-10% ethyl alcohol, 00-1% benzyl alcohol, 0.25-.5mM EDTA, and a citrate-phosphate buffer of pH 7.4-7.8 consisting of 3-50mM citrate and 90-200 mM phosphate for maintaining LCMV specific CTL response in said mammal. The said methods wherein the LCMV specific CTL response is maintained via an osmotic pump implanted in the mammal, or via an insulin pump.

With the exception of the specific peptide antigen and the specific plasmid for inducing LCMV specific CTL response, there is insufficient written description about the structure associated with function of (1) *any* cell-free antigen, (2) *any* protein, (3) *any* peptide, (4) *any* microorganism, (5) *any* nucleic acid encoding *any* undisclosed antigen, and (6) *any* “component” of microorganism cell and wherein said microorganism cell comprises a recombinant nucleic acid encoding or promoting expression said undisclosed antigen for treating *any* disease because any antigen, peptide, protein without the amino acid sequence (SEQ ID NO), and the corresponding nucleic acid has no structure. Given the infinite number of cell-free antigen, protein, peptide, nucleic acid and microorganism, the claimed method of inducing any CTL response using any undisclosed antigen is not adequately described. Further, the specification discloses only the specific method using the specific peptide antigen and the specific plasmid for inducing the LCMV specific CTL response, the method of inducing CTL response toward any undisclosed antigen, protein, peptide, nucleic acid is not adequately described. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co.* 43 USPQ2d 1398.

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

6. Claims 38-51 and 60-62 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The "cell-free" in Claims 38 and 45 represents a departure from the specification and the claims as originally filed. Applicant has not pointed the support for said phrase in the amendment filed 12/14/01.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.
8. Claims 49, and 60-61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "component of a microorganism cell" in claim 49 is indefinite and ambiguous because it is not clear if the "component" is referring to the DNA, the protein, or the cell wall of which microorganism or cell. One of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention.

The "device external to the animal" in claims 60 and 61 is indefinite and ambiguous because it is not clear if the device is a needle, a syringe, a catheter or osmotic pump or insulin pump. One of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:
A person shall be entitled to a patent unless –
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 38-42, 45-46 and 50 are rejected under 35 U.S.C. 102(b) as being anticipated by Issekutz *et al* (Clin Exp Immunol 56(3): 515-23, June 1984; PTO 892).

Issekutz *et al* teach a method of inducing a CTL response such as vaccinia virus specific CTL response in a mammal such as sheep comprising injecting a single bolus dose of a liquid comprising a cell-free antigen such as live vaccinia virus (microorganism) directly into the draining site of the cannulated lymph node (page 516, Materials and methods, in particular) and the reference lymph node inherently maintains the reference antigen in the mammal's lymphatic system over time to induce a CTL response since lymphoblast output 7 days following virus injection and virus specific cytotoxic T cells were detectable up to two weeks (See abstract, Materials and Methods, in particular). Issekutz *et al* further teach that the method is repeated by secondary challenge of the sheep with vaccinia (See page 520, abstract, in particular). The reference antigen is sustained in the lymph node otherwise the reference CTL response would not have last over two weeks. Issekutz *et al* teach that antigen specific CTL are found in the efferent lymph form a single immunized lymph node (See abstract, in particular). Claim 46 is included in this rejection because no immunopotentiator such as adjuvant is injected in the reference method. Thus, the reference teachings anticipate the claimed invention.

11. Claims 38, 40-41, 45-46, and 50-51 are rejected under 35 U.S.C. 102(b) as being anticipated by Grohmann *et al* (J Immunol Methods 137(1): 9-15, March 1991; PTO 892).

Grohmann *et al* teach a method of inducing a CTL response in a mammal such as mice comprising injecting minute amounts of cell-free antigen such as lysate of highly immunogenic murine lymphoma cells bound to nitrocellulose directly into the lymphatic vessel such as the spleen. The reference method of injecting antigen directly into the spleen is the same method as disclosed on page 73, line 20. The reference method induces cell-mediated immunity (CTL response) such as delayed type hypersensitivity (DTH) response in vivo upon footpad challenge and/or lyses of tumor target cell in vitro (See abstract, Materials and methods, in particular). The reference method induces both specific humoral and cell-mediated immunity to minute amounts of antigen (See abstract, in particular). The reference method of delivering the reference antigen is repeated three times at 15-day intervals (See abstract, Materials and Methods, in particular). Grohmann *et al* teach that intrasplenic immunization is useful not only for stimulating the production of antibody but also for the induction of cell-mediated immunity (CTL response) to

antigens that can only be obtained in nanograms amount (See page 14, column 2, last paragraph, in particular). Thus, the reference teachings anticipate the claimed invention.

12. Claims 38-41, 45, and 50 are rejected under 35 U.S.C. 102(b) as being anticipated by Klavinskis *et al* (J Immunol 157(6): 2521-7, Sept 1996; PTO 892).

Klavinskis *et al* teach a method of inducing CTL response in a mammal such as Rhesus macaques by injecting subcutaneously in the proximity of the iliac lymph node of the macaques a liquid comprising a cell-free antigen such as SIVp27:Ty-VLP peptide mixed with aluminum hydroxide that induce a virus-specific CTL response. The reference antigen is delivered in a single bolus dose and repeated at monthly interval (2x) (See Materials and methods, page 2522, in particular). The reference antigen is a component of a microorganism cell such as virus-like particle SIV gag gene encoding p27 fused to yeast transposon Ty that is expressed by the microorganism cell such as yeast (See Materials and Methods, column 2, last paragraph bridging page 2521-2522, in particular). The term “comprising” is open-ended. It expands the liquid in the claimed method to include additional material such as aluminum hydroxide to read on the reference method. Thus, the reference teachings anticipate the claimed invention.

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

14. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 38, 43, 45-46, 48-49 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Issekutz *et al* (Clin Exp Immunol 56(3): 515-23, June 1984; PTO 892) in view of US Pat No. 6,204,250 B1 (of record, March 2001, PTO 892), Coupey *et al* (Cytokine 5(6): 564-9, Nov 1993; PTO 892) and Zinkernagel *et al* (Immunol Rev 156: 199-209, April 1997; PTO 892).

The teachings of Issekutz *et al* have been discussed *supra*.

The claimed invention as recited in claims 43 and 48 differs from the teachings of the reference only that the antigen is delivered in the form of a nucleic acid encoding the antigen.

The claimed invention as recited in claim 46 differs from the teachings of the reference only that the method wherein the induction of cytotoxic T lymphocytes is obtainable independent of immunopotentiator.

The claimed invention as recited in claim 49 differs from the teachings of the reference only that the method wherein the antigen is delivered in the form of a component of a microorganism cell comprises a recombinant nucleic acid encoding said antigen.

The claimed invention as recited in claim 51 differs from the teachings of the reference only that the method further comprises obtaining a sustained CTL response in the mammal and detecting a CTL response in the mammal.

The '250 patent teaches a method of immunizing a mammal such as infant against any target antigen wherein the antigen is delivered in the form of nucleic acid or vector in the host cell that encodes said antigen such as virus or bacteria (See Abstract, column 4, column 7, lines 49-53, claim 14 of '250 patent, in particular). The reference antigen is injected into the infant mammals by any means and route known in the art (See column 8, lines 31-37, in particular). The reference method of inducing cytotoxic T lymphocytes is obtainable independent of immunopotentiator since the reference method injected only the reference antigen such as plasmid encoding NPV1 in physiological saline the absence of immunopotentiator such as adjuvant (See column 9, lines 51, in particular). The reference method is useful for inducing CTL response that can be measured by CTL assay such as 51CR release assay (See column 10, line 31, in particular).

Coupey *et al* teach injection of popliteal lymph node (axillary lymph node) using a glass syringe and intralymph node immunization enables the antigen to trigger the immune system directly, preventing the tissue retention, catabolism and dilution observed with subcutaneous or intravenous injections (See page 567, column 1, paragraph 2, in particular). Coupey *et al* teach

that the reference method is useful in obtaining high titer antigen specific antibodies rapidly with low amounts of antigen (See page 567, column 1, paragraph 2, in particular).

Zinkernagel *et al* teach that antigen presenting cell (APC) with antigens must migrate via the afferent lymph to local lymph nodes (afferent lymph nodes) to present transported antigens to immune cells such as T and B cells in order for T cells to be sensitized to the specific antigen since antigens outside of the lymphoid tissues are immunologically ignored (See page 202, column 2, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to inject directly into the lymph node as taught by Coupey *et al* or Zinkernagel *et al* of any antigen in the form of nucleic acid or vector in host cell encoding the antigen as taught by the '250 patent that encoded the antigen as taught by the Issekutz *et al* for a method of inducing CTL response in a mammal as taught by Issekutz *et al*, Coupey *et al* and Zinkernagel *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '250 patent teaches that the reference method of inducing cytotoxic T lymphocytes is obtainable independent of immunopotentiatiior since the reference method injected only the reference antigen such as plasmid encoding NPV1 in physiological saline the absence of immunopotentiator such as adjuvant (See column 9, lines 51, in particular). Issekutz *et al* teach that antigen specific CTL are found in the efferent lymph form a single immunized lymph node (See abstract, in particular). Coupey *et al* teach that direct injection of antigen to the popliteal lymph node (axillary lymph node) enables the antigen to trigger the immune system directly, preventing the tissue retention, catabolism and dilution observed with subcutaneous or intravenous injections (See page 567, column 1, paragraph 2, in particular). Zinkernagel *et al* teach that antigen presenting cell (APC) with antigens must migrate via the afferent lymph to local lymph nodes (afferent lymph nodes) to present transported antigens to immune cells such as T and B cells in order for T cells to be sensitized to the specific antigen since antigens outside of the lymphoid tissues are immunologically ignored (See page 202, column 2, in particular).

16. Claims 38, 45-47, and 60-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Issekutz *et al* (Clin Exp Immunol 56(3): 515-23, June 1984; PTO 892) in view of US Pat No 5,679,647 (of record, Oct 1997, PTO 892), US Pat No 5,830,452 A (Nov 1998; PTO 892), Coupey *et al* (Cytokine 5(6): 564-9, Nov 1993; PTO 892) and Zinkernagel *et al* (Immunol Rev 156: 199-209, April 1997; PTO 892).

The teachings of Issekutz *et al* have been discussed *supra*.

The claimed invention as recited in claim 47 differs from the teachings of the reference only that the method wherein the antigen is delivered with a cytokine.

The claimed invention as recited in claims 60 and 61 differs from the teachings of the reference only that the method wherein the delivering step further comprises delivering the liquid directly to the lymph node or lymph vessel of the mammal from a device external to the mammal.

The claimed invention as recited in claim 62 differs from the teachings of the reference only that the method wherein the antigen is delivered continuously over a period of time.

The '647 patent teaches a method of inducing CTL response in a mammal such as human by injecting any antigen such as nucleic acid or naked DNA encoding tumor antigen or viral antigen in the form of vector or plasmid mixed with a cytokine such as IL-2 (See column 21, line 11, column 14, lines 18, in particular). The reference method is useful for stimulating antigen specific CTL response in the host (See column 29, lines 51-55, in particular).

The '452 patent teach a method of enhancing CTL response such as enhance anti-tumor efficacy by administering cytokine such as IL-2. The reference cytokine is administered in a bolus dose, in a continuous, repeated or sustained manner from a device external to the mammal such as a computer driven pump (See column 5, lines 57-65, in particular). The reference external device is useful for enhancing the therapeutic index of any compound that is useful to stimulate CTL response such as treating tumors, improving patient compliance and minimizing toxicity (See abstract, in particular).

Coupey *et al* teach injection of popliteal lymph node (axillary lymph node) using a glass syringe and intralymph node immunization enables the antigen to trigger the immune system directly, preventing the tissue retention, catabolism and dilution observed with subcutaneous or intravenous injections (See page 567, column 1, paragraph 2, in particular). Coupey *et al* teach that the reference method is useful in obtaining high titer antigen specific antibodies rapidly with low amounts of antigen (See page 567, column 1, paragraph 2, in particular).

Zinkernagel *et al* teach that antigen presenting cell (APC) with antigens must migrate via the afferent lymph to local lymph nodes (afferent lymph nodes) to present transported antigens to immune cells such as T and B cells in order for T cells to be sensitized to the specific antigen since antigens outside of the lymphoid tissues are immunologically ignored (See page 202, column 2, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include cytokine such as IL-2 that stimulates CTL response, i.e., enhances anti-tumor efficacy or viral cytotoxicity as taught by the '647 patent and the '452 patent in the method of inducing CTL response in a mammal by injecting antigen directly into the lymphatic vessel as taught by Issekutz *et al*, Coupey *et al* and Zinkernagel *et al* using an external device such as a pump as taught by the '452 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '647 patent teaches that antigen such as nucleic acid encoding the target antigen is useful for stimulating antigen specific CTL response against infectious agent an/or tumor in the host (See column 29, lines 51-55, in particular). The '452 patent teaches that cytokine such as IL-2 is useful for stimulating CTL response such as anti-tumor therapy and the therapeutic index of the reference method is enhanced by continuous, repeated or sustained release of IL 2 from a device external to the mammal such as a computer driven pump due to patient compliance and minimize toxicity (See column 5, lines 57-65, in particular). Coupey *et al* teach that direct injection of antigen to the popliteal lymph node (axillary lymph node) enables the antigen to trigger the immune system directly, preventing the tissue retention, catabolism and dilution observed with subcutaneous or intravenous injections (See page 567, column 1, paragraph 2, in particular). Zinkernagel *et al* teach that antigen presenting cell (APC) with antigens must migrate via the afferent lymph to local lymph nodes (afferent lymph nodes) to present transported antigens to immune cells such as T and B cells in order for T cells to be sensitized to the specific antigen since antigens outside of the lymphoid tissues are immunologically ignored (See page 202, column 2, in particular).

17. Claims 38-39, 43, 45-49, and 60-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grohmann *et al* (J Immunol Methods 137(1): 9-15, March 1991; PTO 892) in view of US Pat No. 6,204,250 B1 (of record, March 2001, PTO 892), US Pat No 5,830,452 (Nov 1998, PTO 892), Coupey *et al* (Cytokine 5(6): 564-9, Nov 1993; PTO 892) and Zinkernagel *et al* (Immunol Rev 156: 199-209, April 1997; PTO 892).

The teachings of Grohmann *et al* have been discussed *supra*.

The claimed invention as recited in claim 39 differs from the teachings of the reference only that the method wherein the antigen is delivered directly to a lymph node.

The claimed invention as recited in claims 43 and 48 differs from the teachings of the reference only that the antigen is delivered in the form of a nucleic acid encoding the antigen.

The claimed invention as recited in claim 49 differs from the teachings of the reference only that the method wherein the antigen is provided as a component of a cell that comprises a recombinant nucleic acid encoding or promoting the expression of the antigen.

The claimed invention as recited in claim 47 differs from the teachings of the reference only that the method wherein the antigen is delivered with a cytokine.

The claimed invention as recited in claims 60 and 61 differs from the teachings of the reference only that the method wherein the delivering step further comprises delivering the liquid directly to the lymph node or lymph vessel of the mammal from a device external to the mammal.

The claimed invention as recited in claim 62 differs from the teachings of the reference only that the method wherein the antigen is delivered continuously over a period of time.

The '647 patent teaches a method of inducing CTL response in a mammal such as human by injecting any antigen such as nucleic acid or naked DNA encoding tumor antigen in the form of nucleic acid, vector or plasmid (See column 14, lines 18, in particular). The reference antigen further mixes with a cytokine such as IL-2 (See column 21, line 11, in particular). The reference method is useful for stimulating tumor antigen specific CTL response in the host (See column 29, lines 51-55, in particular).

The '452 patent teach a method of enhancing CTL response such as enhance anti-tumor efficacy by administering cytokine such as IL-2. The reference cytokine is administered in a bolus dose, in a continuous, repeated or sustained manner from a device external to the mammal such as a computer driven pump (See column 5, lines 57-65, in particular). The reference method of using external device is useful for enhancing the therapeutic index of any compound such as

cytokine that is useful to stimulate CTL response such as treating tumors, to improve patient compliance and to minimize toxicity (See abstract, in particular).

Coupey *et al* teach injection of popliteal lymph node (axillary lymph node) using a glass syringe and intralymph node immunization enables the antigen to trigger the immune system directly, preventing the tissue retention, catabolism and dilution observed with subcutaneous or intravenous injections (See page 567, column 1, paragraph 2, in particular). Coupey *et al* teach that the reference method is useful in obtaining high titer antigen specific antibodies rapidly with low amounts of antigen (See page 567, column 1, paragraph 2, in particular).

Zinkernagel *et al* teach that antigen presenting cell (APC) with antigens must migrate via the afferent lymph to local lymph nodes (afferent lymph nodes) to present transported antigens to immune cells such as T and B cells in order for T cells to be sensitized to the specific antigen since antigens outside of the lymphoid tissues are immunologically ignored (See page 202, column 2, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to inject directly into the lymph node as taught by Coupey *et al* or Zinkernagel *et al* of any antigen in the form of nucleic acid or vector in host cell encoding the antigen as taught by the '647 patent along with a cytokine such as IL-2 that stimulates CTL response, i.e., enhances anti-tumor efficacy as taught by the '647 patent and the '452 patent in the method of inducing CTL response in a mammal by injecting antigen directly into the lymphatic vessel as taught by Grohmann *et al*, Coupey *et al* continuously using an external device such as a pump as taught by the '452 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '647 patent teaches that antigen such as nucleic acid encoding the target antigen is useful for stimulating antigen specific CTL response against infectious agent an/or tumor in the host (See column 29, lines 51-55, in particular). The '452 patent teaches that cytokine such as IL-2 is useful for stimulating CTL response such as anti-tumor therapy and the therapeutic index of the reference method is enhanced by continuous, repeated or sustained release of IL 2 from a device external to the mammal such as a computer driven pump due to patient compliance and minimize toxicity (See column 5, lines 57-65, in particular). Coupey *et al* teach that direct injection of antigen to the popliteal lymph node (axillary lymph node) and intralymph node injection enables

the antigen to trigger the immune system directly, preventing the tissue retention, catabolism and dilution observed with subcutaneous or intravenous injections (See page 567, column 1, paragraph 2, in particular). Zinkernagel *et al* teach that antigen presenting cell (APC) with antigens must migrate via the afferent lymph to local lymph nodes (afferent lymph nodes) to present transported antigens to immune cells such as T and B cells in order for T cells to be sensitized to the specific antigen since antigens outside of the lymphoid tissues are immunologically ignored (See page 202, column 2, in particular). Grohmann *et al* teach that direct injection of antigen into the lymphatic vessel such as the spleen induces both specific humoral and cell-mediated immunity to minute amounts of antigen (See abstract, in particular).

18. Claims 38, 43, 45, 48, 49, and 60-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klavinskis *et al* (J Immunol 157(6): 2521-7, Sept 1996; PTO 892) in view of US Pat No. 6,204,250 B1 (of record, March 2001, PTO 892), Coupey *et al* (Cytokine 5(6): 564-9, Nov 1993; PTO 892) and Zinkernagel *et al* (Immunol Rev 156: 199-209, April 1997; PTO 892).

The teachings of Klavinskis *et al* have been discussed *supra*.

The claimed invention as recited in claims 43 and 48 differs from the teachings of the reference only that the antigen is delivered in the form of a nucleic acid encoding the antigen.

The claimed invention as recited in claim 49 differs from the teachings of the reference only that the method wherein the antigen is provided as a component of a cell that comprises a recombinant nucleic acid encoding or promoting the expression of the antigen.

The claimed invention as recited in claims 60 and 61 differs from the teachings of the reference only that the method wherein the delivering step further comprises delivering the liquid directly to the lymph node or lymph vessel of the mammal from a device external to the mammal.

The claimed invention as recited in claim 62 differs from the teachings of the reference only that the method wherein the antigen is delivered continuously over a period of time.

The '250 patent teaches a method of immunizing a mammal such as infant against any target antigen wherein the antigen is delivered in the form of nucleic acid or vector in the host cell that encodes said antigen such as virus or bacteria (See Abstract, column 4, column 7, lines 49-53, claim 14 of '250 patent, in particular). The reference antigen is injected into the infant mammals by any means and route known in the art (See column 8, lines 31-37, in particular).

The reference method of inducing cytotoxic T lymphocytes is obtainable independent of immunopotentiator since the reference method injected only the reference antigen such as

plasmid encoding NPV1 in physiological saline the absence of immunopotentiator such as adjuvant (See column 9, lines 51, in particular). The reference method is useful for inducing CTL response that can be measured by CTL assay such as ^{51}Cr release assay (See column 10, line 31, in particular).

The '079 patent teaches a method of enhancing CTL response against viral and bacterial infection by administering cytokine such as IL-2 (See entire document, abstract, in particular) and intermittent IL-2 therapy with continuous infusion of IL-2 is useful for broaden the antigen specific repertoire of the immune system during gene therapy (See column 27, lines 32-35, in particular).

The '452 patent teach a method of enhancing CTL response by administering cytokine such as IL-2. The reference cytokine is administered in a bolus dose, in a continuous, repeated or sustained manner from a device external to the mammal such as a computer driven pump (See column 5, lines 57-65, in particular). The reference method of using external device is useful for enhancing the therapeutic index of any compound such as cytokine that is useful to stimulate CTL response such as treating tumors, to improve patient compliance and to minimize toxicity (See abstract, in particular).

Coupey *et al* teach injection of popliteal lymph node (axillary lymph node) using a glass syringe and intralymph node immunization enables the antigen to trigger the immune system directly, preventing the tissue retention, catabolism and dilution observed with subcutaneous or intravenous injections (See page 567, column 1, paragraph 2, in particular). Coupey *et al* teach that the reference method is useful in obtaining high titer antigen specific antibodies rapidly with low amounts of antigen (See page 567, column 1, paragraph 2, in particular).

Zinkernagel *et al* teach that antigen presenting cell (APC) with antigens must migrate via the afferent lymph to local lymph nodes (afferent lymph nodes) to present transported antigens to immune cells such as T and B cells in order for T cells to be sensitized to the specific antigen since antigens outside of the lymphoid tissues are immunologically ignored (See page 202, column 2, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to inject antigen in the form of nucleic acid that encodes the antigen of interest as taught by the '250 patent directly into the lymph node or lymphatic vessel as taught by the Klavinskis *et al*, Coupey *et al* and Zinkernagel *et al* along with a cytokine such as IL-2 as taught by the '079 patent and the '452 patent in a bolus dose, continuous, repeated or sustained

manner from a device external to the mammal such as a computer driven pump as taught by the '452 patent (See column 5, lines 57-65, in particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Klavinskis *et al* teach that injecting cell-free antigen such as SIVp27:Ty-VLP peptide subcutaneously in the proximity of the iliac lymph node of the macaques induces a virus-specific CTL response. Coupey *et al* teach injection of popliteal lymph node (axillary lymph node) or intralymph node immunization enables the antigen to trigger the immune system directly, preventing the tissue retention, catabolism and dilution observed with subcutaneous or intravenous injections (See page 567, column 1, paragraph 2, in particular). Zinkernagel *et al* teach that antigen presenting cell (APC) with antigens must migrate via the afferent lymph to local lymph nodes (afferent lymph nodes) to present transported antigens to immune cells such as T and B cells in order for T cells to be sensitized to the specific antigen since antigens outside of the lymphoid tissues are immunologically ignored (See page 202, column 2, in particular). The '079 patent teaches that IL-2 is useful for enhancing CTL response against viral and bacterial infection (See entire document, abstract, in particular). The '452 patent teach that cytokine such as IL-2 enhances CTL response against tumor and continuous infusion using an external device such as a computer driven pump is useful for enhancing the therapeutic index, improving patient compliance and minimizing toxicity (See abstract, in particular). The '250 patent teaches that immunizing a mammal such as infant against any target antigen in the form of nucleic acid encoding the reference antigen is useful for inducing cell mediated immune response (See Abstract, column 7, lines 49-53, claim 14 of '250 patent, in particular).

19. Claim 44 appears to be free of prior art.
20. No claim is allowed.
21. **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the

mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.
23. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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October 20, 2003

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